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| EXAMINER | |
|---|---|
| TON, THAIAN N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/980,557 | LOI ET AL. | |
| | Examiner | Art Unit | |
| | Thai-An N Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-38 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-38 is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Claims 1-38 are pending and under current examination.

### *Specification*

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See p. 12, line 17.

### *Claim Objections*

Claims 13-17 are objected to because of the following informalities: the claims recite the term "genetical modification" which appears to be a misspelling of "genetic modification". Appropriate correction is required.

Claim 14 is objected to because of the following informalities: the word "heterologous" is misspelled in line 3 of the claim. Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 34 and 35 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to a reconstructed non-human animal embryo [claim 35] and a non-human animal [claim 36]. These are non-statutory because they read on naturally occurring animal embryos and animals.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for reconstructing an ovine embryo comprising transferring a G1 or G0 diploid nucleus from an ovine donor cell or a G1 or G0 diploid donor ovine cell into an enucleated metaphase II ovine oocyte, wherein the chromatin of the donor ovine nucleus is subjected to denaturing conditions before transfer into the recipient ovine oocyte, activating the resulting nuclear transfer unit, culturing the resulting NT unit to form blastocysts, transferring the blastocysts into a ovine surrogate mother and allowing the blastocysts to develop to term to form an ovine. The specification does not reasonably provide enablement for methods for reconstructing an animal embryo of a non-human mammalian species comprising transferring into a recipient cell a diploid nucleus from a donor

cell, or the donor cell including said nucleus, wherein the donor cell is a G1 or G0 cell from a non-human mammalian species, and the recipient cell is an enucleated metaphase II oocyte of a non-mammalian species, wherein the chromatin within the nucleus is subject to denaturing conditions before transfer into the recipient cell, wherein the recipient cell is further culture *in vitro* or *in vivo* and the animal embryo is cultured to obtain blastocysts which are then transferred into a suitable recipient animal, wherein the embryo is allowed to develop to term. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to methods for reconstructing an animal embryo of a non-human mammalian species comprising transferring into a recipient cell a diploid nucleus from a donor cell, or the donor cell including said nucleus, wherein the donor cell is a G1 or G0 cell from a non-human mammalian species, and the recipient cell is an enucleated metaphase II oocyte of a non-mammlain species, wherein the chromatin within the nucleus is subject to denaturing conditions before transfer into the recipient cell, wherein the recipient cell is further culture *in vitro* or *in vivo*. In further embodiments, the animal embryo is cultured to obtain blastocysts which are then transferred into a suitable recipient animal, wherein the embryo is allowed to develop to term and can be further bred.

The specification teaches the heat denaturation of ewe granulosa cells, freeze-dried and then re-hydrated for use in NT. See Example 1. Oocytes were collected from ewes, matured *in vitro*, and MII oocytes were enucleated and injected with the donor granulosa cells. The resulting NT unit was then activated by ionomycin, and the reconstructed embryos were cultured *in vitro*. See Example 2. Resulting blastocysts were then transferred into recipient ewes for development to term and one offspring [2640] was carried to term. See Table 2.

The claimed invention is not enabling for the breadth of the claims because they recite producing a non-human mammalian embryo or allowing the non-human mammalian embryo to develop to term. The specification teaches that the claimed invention can be used in all non-human mammalian species, such as cattle, sheep, goats, pigs, mice, etc. See p. 11, lines 20-24. However, the specification fails to provide sufficient teaching that any mammalian embryo, other than the exemplified ovine embryo and the resulting sheep, could be produced by the claimed method and one of skill would not be able to rely upon the state of the art for specific teachings with regard to the generation of mammalian embryos by NT, for the breadth claimed, because NT protocols are species-specific, and thus, require specific guidance to enable them. Westhusin *et al.* (**Theriogenology**, Vol. 55, pp. 35-49, 2001) review the state of the art of cloning. They state that, "Without a doubt, one of the major factors influencing the probability of cloning a specific animal is species. While the basic approach involving nuclear transfer may be similar, the

specific materials and methods utilized for cloning one species of animal do not automatically apply across different species." (see p. 36, 4th paragraph). Westhusin *et al.* further state that the factors to consider when cloning animals by nuclear transfer include acquisition of mature ova, enucleation of mature ova, nuclear transfer into the enucleated ova, activation of the newly formed embryo, culturing the embryo *in vitro* and transferring the embryo into a surrogate mother. Furthermore, these techniques and the efficacy of these techniques will vary from species to species. (see p. 36-37, bridging paragraph). Westhusin *et al.* clearly teach the unpredictable state of the art of nuclear transfer with regard to the unpredictable factors such as species difference, donor cells and genetic modifications. As the specification fails to provide any guidance or teaching for the production of all species of embryos and cloned animals, one of skill would not be able to rely upon the state of the nuclear transfer art to attempt to produce such animals.

It is further noted that the claims fail to recite an activation step for the resulting NT unit. It is well-known in the nuclear transfer art that activation of the resulting nuclear transfer unit must take place in order to effect further development. Dinnyés *et al.* [**Cloning & Stem Cells**, 4 :81-92 (2002)] report on the state of the art of somatic cell nuclear transfer, stating that, "NT is a complex procedure and each step effects the overall efficiency. The unpredictability of the technology due to biological variation of the recipient oocytes and the donor cells is

difficult to control. Therefore, standardization of the steps is important in order to obtain consistent results." See p. 83, 1st column, 2nd full ¶. With particular regard to the importance of activation of oocytes, Dinnyés state that, "In NT, the lack of sperm-induced fertilization steps necessitate the application of an artificial activation in order to trigger further development." See p. 83, 2nd column, last ¶. Although the specification teaches that the NT units are activated by ionomycin, the claims fail to recite such a step and without an activation step, the NT unit would fail to develop further, as required by the claims.

Certain embodiments of the claimed invention are directed to the transfer of blastocysts into a surrogate mother. However, the breadth of these claims encompass the implantation of cultured nuclear transfer units into surrogate mothers of different species. However, such implantation is not predictable, as Fehilly *et al.* (**Nature**, Vol. 307, 16 February 1984) teach that often two unrelated species cannot carry a live hybrid fetus to term due to factors such as interspecific pregnancies, placental abnormalities and maternal immunological reaction against foreign antigens of the conceptus which would be the cause of immediate abortion (see p. 634, 1st column, 2nd paragraph). Fehilly *et al.* summarize experiments for the production of such animals, and show an extremely low percentage of full term young (see Table 1, p. 635). Although Fehilly *et al.* show that is possible to produce embryos that have been implanted into surrogate mothers of a foreign species, it is clearly an unpredictable process.

Accordingly, the Examiner has clearly provided evidence for the unpredictability of the NT art, as such, specific guidance must be provided by the specification. However, the instant specification fails to provide teachings or guidance to overcome these art-recognized unpredictabilities and one of skill in the art could not rely on the state of the art, because it is replete with teachings to show NT's unpredictability for the generation of NT embryos from any species of mammal as broadly claimed.

Particular claims are directed to methods of generating transgenic animals, and transgenic animals. However, the state of the art of generating transgenic animals is such that the resulting phenotype of the transgenic animal would not be predictable. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappell et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). Mullins et al (1993) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into difference species of animal has been reported to given divergent phenotypes (Mullins et al (1993) Hypertension 22, page 631, col. 1, parag. 1, lines 14-17). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by

case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) J. Biotech. 34, page 281). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall (1996) Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). Mullins et al.(1996) disclose that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (Mullins et al (1996) J. Clin. Invest. 98, page S39, Summary). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997), Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron (1997), Molec. Biol. 7, page 256, lines 10-13). Further, Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, parag. 1, lines 1-7). With

regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann (1997) Transg. Res. 7, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). While the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic non-human animal, it would have required undue experimentation to the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype. The specification fails to provide teachings or specific guidance to overcome the above-described unpredictabilities, in order to successfully carry out the claimed methods of NT to produce a transgenic animal with a specific phenotype, and as such, the claims are not enabling.

Accordingly, in view of the undeveloped and unpredictable state of the art with regard to NT, and the unpredictable state of the art for the generation of transgenic animals, with particular regard to the resulting phenotype, it would have required undue experimentation for one of skill in the art to carry out the claimed invention.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, as written, is incomplete. The claim is directed to a process for reconstructing an animal embryo, however, the claim fails to provide specific method steps for generating the embryo. For example, it is unclear how culturing an NT unit relates to the preamble, "A method for reconstructing an animal embryo." Claims 2-38 depend from claim 1.

Claim 2 is unclear. The claim recites that the denaturing conditions can be "heat-treatment, or any combination of temperature, pH, ionic strength and other chromatin denaturing agent". It is unclear what combination the claim is referring to. It is unclear if the claims are attempting to recite a Markush group because they do not recite the conditions in the alternative; if so, they should be written as an appropriate Markush group. See MPEP §2173.05(h). Further, it is suggested the claims recite, "the denaturing conditions ..." in line 1 of the claim for clarity. Claims 3-6 depend from claim 2.

Claim 21 is unclear. The claim recites that the denaturing treatment is carried out on the nucleus inside the donor cells. This language is not clear because 1) if the NT process is using a donor cell then the denaturing treatment would be carried out on the cell and if 2) the NT process is carried out on a nucleus, then would the process be carried out prior to removal of the nucleus from the donor cell?

Furthermore, if a donor cell were being used in the NT process, the whole cell would be denatured. Clarification and/or amendment to the claim is required.

Claim 22 is unclear for the reasons stated for claim 21. The claim recites that the denaturing process is carried out on the nucleus outside of the donor cell. Is this referring to a nucleus that has been taken out of the donor cell? Clarification and/or amendment to the claim is required.

Claim 24 is incomplete. The claim recites that NT is carried out by injection. It is unclear what is being injected.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by Blakely *et al.* [**The Science of Animal Husbandry**, Prentice-Hall, Inc., 5th Edition, 1990, pages 257-261].

The claim is directed to an animal resulting from the process according to claim 28. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do

not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Blakely teach various breeds of sheep, see for example, p. 259. Note that because the claim is a product-by-process claim, the claim is properly interpreted as a non-human mammal. Accordingly, Blakely anticipate the claimed invention.

Claims 34 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Gómez *et al.* [**Theriogenology**, 49:1143-1154 (15 April 1998)].

The claims are directed to a reconstructed animal embryo produced by NT, and an animal produced by NT. Note that the claims are product-by-process claims, see *supra*.

Gómez teach generation of sheep embryos [see p. 1147, 1st full ¶] and ewes [see p. 1147, 2nd full ¶]. Because the claims are product-by-process claims, they are properly interpreted as a mammalian embryo and a mammal. Accordingly, Gómez anticipate the claimed invention.

Claims 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Schnieke e*t al.* [**Science**, 278:2130-2133 (1997)].

The claims are directed to transgenic animals resulting from a NT method, wherein the transgenic animal is selected from the group consisting of laboratory animals and ungulates. The claims are product-by-process claims, see *supra.*

Schnieke teach the production of transgenic lambs expressing human factor IX, by nuclear transfer. See *Abstract.* Because the claims are product-by-process claims, they are properly interpreted as transgenic animals. Accordingly, Schnieke anticipate the claimed invention.

*Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT

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